Combinaison de la glucosamine et du MSM plus efficace dans l'ostéoarthrite

Randomised, double-blind, parallel, placebo-controlled study of oral glucosamine, methylsulfonylmethane and their combination in osteoarthritis.
Usha et al., 2004 (Clinical Drug Investigation)

L'arthrose est une maladie articulaire dégénérative et la cause la plus fréquente de problèmes articulaires chez les personnes âgées. C'est principalement une **maladie du cartilage, avec des modifications secondaires de l'os**. Le Paracétamol et les AINS sont fréquemment utilisés dans l'arthrose, mais il y a peu de preuves que ces agents peuvent affecter la pathologie sous-jacente de cette maladie. De plus, des effets secondaires fréquents empêchent l'utilisation à long terme des AINS.

Les médicaments qui peuvent ralentir ou contrer la dégénérescence progressive du cartilage dans l'arthrose sont extrêmement intéressant. La chondroprotection est de première importance à cet égard. **La glucosamine (Glu) est l'un des 'slow-acting drugs' dans l'arthrose** et est un agent **chondroprotecteur efficace** avec des effets anti-inflammatoires légers. De plus, **le méthylsulfonylméthane (MSM)**, la forme oxydée du diméthylsulfoxyde, est également un agent anti-inflammatoire naturel qui a également des **effets analgésiques efficaces**.

Cette recherche vise à étudier l'effet de la prise orale de la glucosamine, du MSM ou de leur combinaison sur l'arthrose du genou.

<u>Résultats et Conclusion</u>:

La recherche a montré que les **effets bénéfiques de la glucosamine sont devenus cliniquement pertinents après deux semaines de traitement** et ont conduit à une amélioration significative à partir de la quatrième semaine. **Aussi avec un traitement de MSM**, une réduction significative de la douleur et une amélioration de la mobilité sont apparues après deux semaines.

Lorsque la glucosamine et le MSM étaient administrés simultanément, une diminution très significative de l'intensité de la douleur et de l'enflure pouvait être observée. De plus, cette **réduction de la douleur et de l'enflure due à la combinaison de la glucosamine et du MSM était significativement meilleure que les thérapies individuelles** après 12 semaines de traitement (Figure 1).

La faible toxicité, combinée à l'efficacité pour réduire la douleur et l'enflure, **démontre l'utilité de la glucosamine et du MSM dans le traitement de l'arthrose pour améliorer la fonctionnalité articulaire**.

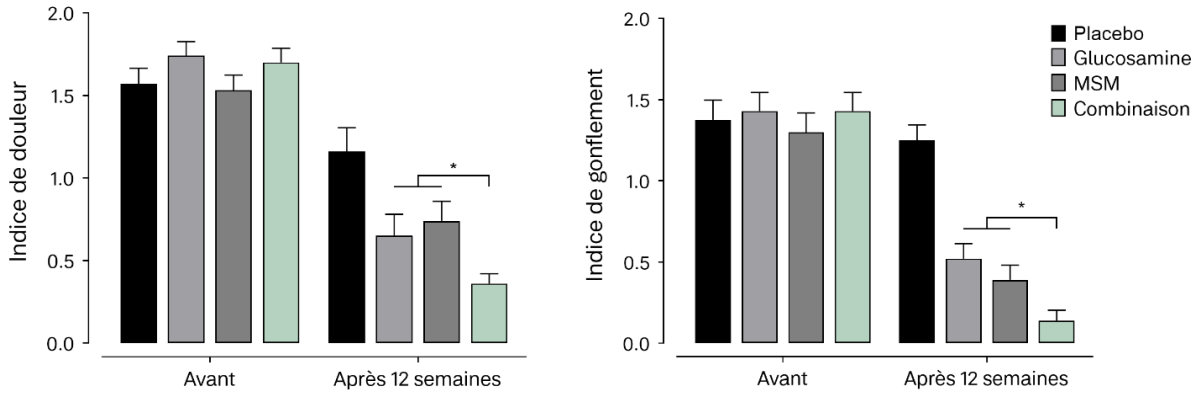

Figure 1 | L'effet de la glucosamine, du MSM ou leur combinaison dans le traitement de l'arthrose. La douleur et le gonflement du genou ont été considérablement réduits par la prise de la glucosamine ou du MSM par rapport au groupe placebo. Une prise combinée a entraîné une réduction encore plus grande de la douleur et de l'enflure après 12 semaines de traitement. * $p < 0.05$

Kasteelhoek 12
B-8730 Beernem
T +32 50 598 881
BE 0880.544.917
www.pures.be
info@pures.be

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Randomised, Double-Blind, Parallel, Placebo-Controlled Study of Oral Glucosamine, Methylsulfonylmethane and their Combination in Osteoarthritis

P.R. Usha and *M.U.R. Naidu*

Department of Clinical Pharmacology and Therapeutics, Nizam's Institute of Medical Sciences, Hyderabad, India

Abstract

Objective: Glucosamine, classified as a slow-acting drug in osteoarthritis (SADOA), is an efficacious chondroprotective agent. Methylsulfonylmethane (MSM), the isoxidised form of dimethyl-sulfoxide (DSMO), is an effective natural analgesic and anti-inflammatory agent. The aim of this study was to compare the efficacy and safety of oral glucosamine (Glu), methylsulfonylmethane (MSM), their combination and placebo in osteoarthritis of the knee.

Patients and design: A total of 118 patients of either sex with mild to moderate osteoarthritis were included in the study and randomised to receive either Glu 500mg, MSM 500mg, Glu and MSM or placebo capsules three times daily for 12 weeks. Patients were evaluated at 0 (before drug administration), 2, 4, 8 and 12 weeks post-treatment for efficacy and safety. The efficacy parameters studied were the pain index, the swelling index, visual analogue scale pain intensity, 15m walking time, the Lequesne index, and consumption of rescue medicine.

Results: Glu, MSM and their combination significantly improved signs and symptoms of osteoarthritis compared with placebo. There was a statistically significant decrease in mean (± SD) pain index from 1.74 ± 0.47 at baseline to 0.65 ± 0.71 at week 12 with Glu ($p < 0.001$). MSM significantly decreased the mean pain index from 1.53 ± 0.51 to 0.74 ± 0.65, and combination treatment resulted in a more significant decrease in the mean pain index (1.7 ± 0.47 to 0.36 ± 0.33; $p < 0.001$). After 12 weeks, the mean swelling index significantly decreased with Glu and MSM, while the decrease in swelling index with combination therapy was greater (1.43 ± 0.63 to 0.14 ± 0.35; $p < 0.05$) after 12 weeks. The combination produced a statistically significant decrease in the Lequesne index. All treatments were well tolerated.

Conclusion: Glu, MSM and their combination produced an analgesic and anti-inflammatory effect in osteoarthritis. Combination therapy showed better efficacy in reducing pain and swelling and in improving the functional ability of joints than the individual agents. All the treatments were well tolerated. The onset of

analgesic and anti-inflammatory activity was found to be more rapid with the combination than with Glu. It can be concluded that the combination of MSM with Glu provides better and more rapid improvement in patients with osteoarthritis.

Osteoarthritis, a degenerative joint disease, is the most common condition to affect human joints, and is a major cause of morbidity and disability in the elderly. It is primarily a disorder of cartilage with secondary changes in bone. Although paracetamol and NSAIDs are widely used in the management of osteoarthritis, there is limited evidence that they actually improve the underlying pathology of the disease. Adverse drug reactions are common with NSAIDs, and this factor limits their long-term use.

Drugs that may prevent or retard the progression of articular cartilage breakdown in osteoarthritis are now receiving attention. Chondroprotection is a new field in the management of osteoarthritis that is designed to improve cartilage repair as well as enhance joint remodelling.[1]

Glucosamine (Glu), an amino monosaccharide, is an intermediate substrate used in the synthesis of glycosaminoglycan and proteoglycans by articular cartilage. The molecule administered as Glu also acts as the provider of sulfate ions for the synthesis of chondroitin sulfate and keratin sulfate.[2] Glu is classified as a slow-acting drug in osteoarthritis (SADOA), and stands out as the most efficacious chondroprotective agent currently available.[3] Furthermore, glucosamine protects the cartilage from the metabolic impairment provoked by some NSAIDs, as well as the chondrocytes from the damaging action of high-dose corticosteroids.[4] Finally, Glu has shown mild anti-inflammatory activities through a mechanism of action other than the inhibition of the biosynthesis of prostaglandins.[4]

Methylsulfonylmethane (MSM) is the oxidised form of dimethyl-sulfoxide (DSMO), a natural, organic form of sulphur. MSM is a much more stable organic sulphur compound with medicinal properties equal to those of DSMO, but without the odour and skin irritation complications of the latter. MSM is an effective natural analgesic. It blocks the inflammatory process and enhances the activity of cortisol, a natural anti-inflammatory hormone produced in the body. MSM is considered to be one of the least toxic substances in biology, similar in toxicity to water. MSM, when administered to human volunteers in a dose of 1g per kg bodyweight for 30 days, did not produce any toxic effects.[5]

MSM, also known as dimethyl-sulfone, is derived from DMSO. DMSO is a pungent solvent that has been used as an application for pain relief over arthritic joints.[6] MSM has the advantage of being odourless and can be taken easily orally in the form of a pill or a powder. Both these agents appear to have some beneficial effects on arthritic joints.[7] The optimal dosing of MSM is not known, but 1–2g twice daily is recommended.

DMSO can scavenge (OH-) free radicals, a primary trigger in the inflammatory process, and passes through membranes easily.[8] Neutrophil-mediated depolymerisation with associated release of (OH-) is theorised to contribute to the breakdown of joint tissue in inflammatory arthritic conditions.[9] DSMO has the potential to facilitate the transport of other drugs and substances across membranes. It is possible that DMSO is efficacious in the treatment of pain,[10] inflammation,[11,12] arthritis,[12,13] wound healing,[14] burns[15] and amyloidosis.[16] Because sulphur is needed for the formation of connective tissue, MSM has been studied for its use in treating arthritis. The concentration of sulphur in arthritic cartilage has been shown to be one-third the level of normal cartilage.[17]

Thus, the present study was designed with the aim of comparing the efficacy and safety of oral Glu, MSM and their combination versus placebo in the management of osteoarthritis of the knee.

Patients and Methods

Patients

All the patients enrolled in the present study were recruited from the outpatient division of the Nizam's Institute, Hyderabad, India. Males or females between the ages of 40 and 70 years, with radiological evidence of osteoarthritis of the knee, a minimum duration of symptoms of at least 6 months, not receiving any NSAIDs over the previous 2 weeks, and a Lequesne index score between 8 and 18 points, were eligible for inclusion in the study.

Patients were excluded from the study if they had participated in a clinical trial within the last 30 days; had severe osteoarthritis; were taking any other anti-inflammatory drugs/physiotherapy or any drug from an alternative system of medicine; had a psychiatric disorder or other condition that might interfere with the patient's self-assessment ability; unstable diabetes mellitus; primary inflammatory painful conditions of the knee; gastrointestinal disorders like peptic ulcer; recent injuries to the knee; bronchial asthma; were pregnant or lactating mothers; or if they had had radiographic findings classed as less severe than grade 1. Patients who had intra-articular treatment with any product and arthroscopic procedures within 6 months before the start of the study were also excluded.

One hundred and eighteen patients of either sex between the ages of 40 and 70 years with mild-to-moderate osteoarthritis were enrolled in the study after fulfilling the inclusion and exclusion criteria. Osteoarthritis of the knee was defined according to the Lequesne diagnostic criteria,[18] which include both clinical and radiological criteria.

The study protocol was approved by the Institutional Review Board. Patients declared their willingness to participate in the study once the details of the study and the treatment had been explained to them. All patients enrolled for the study gave written informed consent for study participation. NSAIDs, corticosteroids or any drugs from alternative types of medicine and physical therapy were not allowed during the study period. Paracetamol was allowed as rescue medicine as and when needed. Other treatments for concomitant diseases were permitted and recorded in the diary card that was provided to the patients.

At enrolment, patients underwent a full medical examination including a medical history, with particular emphasis on the involved knee joint(s) and the outcome of past treatment. Radiographs in the anterior-posterior and lateral views were taken of the most affected knee joint. The radiological staging was done according to Kellgren and Lawrence[19] by the radiologist. Grade 0 indicated no arthropathy, while grade 4 indicated severe arthropathy. Most of the patients had a Kellgren score between 1 and 3.

Study Design and Drug Administration

This was a randomised, double-blind, parallel, placebo-controlled study. Patients were randomised into four groups to receive: a Glu 500mg capsule along with matching placebo of MSM, one capsule each three times a day (group 1); MSM 500mg capsule, along with a Glu matching placebo, one capsule each three times daily (group 2); one capsule each of Glu and MSM three times daily (group 3); or two capsules three times daily of placebo identical to Glu and MSM capsule (group 4). All the capsules were identical to maintain double-blindness and were supplied by Healers Limited, Chennai, India. Randomisation was done according to a block design of a total of five blocks with 24 subjects in each block. Most of the patients were taking NSAIDs off and on, although not on a continuous basis. However, some of them (about 25%) did not take NSAIDs, but used local analgesic gels and physiotherapy. Patients were withdrawn from NSAIDs 2 weeks prior to study enrolment.

The test drugs were given daily for 12 weeks after ensuring that all patient recruitment criteria were met. Patients were evaluated at 0 (before drug administration) and at 2, 4, 8 and 12 weeks post-treatment for efficacy and safety parameters. The efficacy parameters were assessed on the most affected knee joint (noted at baseline), which was evaluated throughout the study period.

Efficacy Parameters

The pain and swelling indices were noted on 4-point scales, where 0 = no pain or swelling and 3 = severe incapacitating pain and marked swelling, respectively, and were recorded by the physician. Pain was also assessed using a 0–100mm visual analogue scale (VAS) where 0 = no pain and 100 = pain as severe as can be. Joint mobility was also scored on a 4-point scale where 0 = no restriction of joint movement and 3 = severe restriction. Numerous trials have validated the visual analogue scale as a means of evaluating pain intensity, especially for subjective knee complaints.[20,21] Walk time, which is a measure of lower extremity function in musculoskeletal disease, was assessed by the 15m walking time (in seconds). The clinical functional status was assessed by the algo-functional index (Lequesne index), which consists of three components: (a) pain or discomfort; (b) maximum distance walked; and (c) activities of daily living. Higher values indicate greater severity. The main outcome measures were pain intensity assessed by VAS (as marked by the patient), joint mobility, patients' and physicians' global assessment, and the Lequesne index.

Paracetamol in 500mg tablets was given along with the study drug and was allowed to be used as rescue medicine in cases of unbearable pain. The patient was instructed to record the number of paracetamol tablets consumed each day in the diary card, which was reviewed at each visit. A fresh diary card was given to the patient at each visit. They were allowed a maximum of four tablets per day. The number of paracetamol tablets consumed served as the secondary efficacy variable.

Safety was monitored by medical history, physical examination, blood pressure and pulse rate at each visit. Routine biochemical laboratory parameters, liver function and renal function tests were performed before and after every 4 weeks of therapy. Side effects were assessed at each visit by the investigator asking the patient if they had experienced any changes in their physical symptoms since the previous visit. The occurrence of adverse events was documented in the case record form (CRF) and either reported spontaneously by the patient or by general questioning during the study period. It included onset and duration, and was classified according to severity into mild, moderate, severe or serious, where: mild = no interference with usual activities; moderate = significant interference with usual activities; severe = prevents usual activities; and serious = fatal, life threatening, permanently disabling and/or requiring inpatient hospitalisation.

Furthermore, at each visit patients were asked about any intercurrent illness and therapeutic interventions, which was recorded in the CRF.

Compliance with Therapy

Compliance with the dosage regimen was checked by pill counting. At each visit, patients were asked about all medications taken including background additional medications. Patients who had not taken >80% of the prescribed total study medication were considered 'noncompliant'. Trial medication capsules were counted at each visit to monitor compliance.

Compliance was measured using a 4-point scale: 3 = excellent (drug consumption >90%), 2 = good (drug consumption 81–90%), 1 = fair (drug consumption 65–80%), 0 = poor (drug consumption <65%). Any patient who withdrew or was a dropout had this recorded in the CRF, including the reason for the discontinuation.

At the end of the study, patients' and investigators' global evaluations were performed using a 4-point scale, where 0 = a poor response, 1 = fair, 2 = good and 3 = excellent.

Statistical Analysis

All the data are presented as mean ± SD. Statistical evaluation was done using SAS version 4.1 and Prism graph pad version 2.1 software. Demographic data were compared between groups using Student's t-test. The sample size was calculated based on the minimum level of significance, which was set at 0.05, with a 95% confidence interval (CI) at 80% power. We calculated that an absolute difference of 20% on the VAS between the active treatments and placebo should be detectable if we evaluated 120 participants, a power of 80%, and an alpha value of

Table I. Demographic data of patients with mild-to-moderate osteoarthritis in each of the treatment groups. The ratio of male to female patients along with the mean duration of illness is provided. Values are given as mean ± SD

Parameter	Glu (n = 30) [18F; 12M]	MSM (n = 30) [22F; 8M]	Glu + MSM (n = 30) [20F; 10M]	Placebo (n = 28) [16F; 12M]
Age (y)	52 ± 8	51 ± 8	52 ± 7	50 ± 9
Height (cm)	161 ± 4	160 ± 3	161 ± 4	160 ± 4
Weight (kg)	69 ± 7	64 ± 10	67 ± 7	65 ± 10
Symptom duration (mo)	38 ± 22	35 ± 22	38 ± 22	35 ± 23

F = female; **Glu** = glucosamine; **M** = male; **MSM** = methylsulfonylmethane.

0.05. The principal analysis for efficacy was based on the comparison of the responder rates between treatments. 'Responders' to treatment were considered to be those patients with a decrease in the Lequesne index of at least three points from the baseline value, together with an investigator overall judgement of efficacy rated 'good' or 'fair'. This analysis was performed using Fisher's two-tailed test. Data were analysed on an intent-to-treat basis, and all patients who received at least one dose of the drug were included for analysis. If there were missing values, the last datapoint was carried forward. ANOVA was used for the Lequesne index, pain and swelling index, and intake of paracetamol. To test for statistically significant intergroup differences, the Mann-Whitney U-test was used for categorical variables, and the two-tailed independent Student's t-test was used for continuous variables.

Results

Of 118 patients enrolled, 28 patients were randomised to the placebo group, while Glu was administered to 30 patients, MSM to 30 patients, and a combination of Glu and MSM to a further 30 patients. The demographic data of the participating patient population is shown in table I. There were no statistically significant differences between any of the baseline characteristics between the groups. They were well matched with respect to demographic data, duration of arthritis, baseline score on VAS, concomitant use of analgesics, and radiographic stage. All participants met the criteria for knee osteoarthritis as described by the American College of Rheumatology.[22] Four patients in the placebo group and three patients each in the Glu and MSM groups and two in the combination group were lost to follow-up after 4 weeks' therapy. As this was an intent-to-treat analysis, the last data were carried forward for analysis.

Evaluation of Efficacy Parameters

In order to compare the clinical efficacy of Glu, MSM, a combination of Glu and MSM, and placebo, all patients were clinically evaluated to observe the effect on various efficacy parameters before and at the end of 2, 4, 8 and 12 weeks of therapy. The baseline characteristics of patients in all groups were similar, and there was no difference in the baseline efficacy parameters among all groups. Administration of Glu, MSM and their combination significantly improved the efficacy parameters compared with placebo.

The effect on the pain and swelling indices were used to evaluate the anti-inflammatory effect, and are shown in figure 1 and figure 2. Placebo did not show any significant change in the mean pain index from 0 to 12 weeks (1.57 ± 0.5 to 1.16 ± 0.76), while on the other hand there was a statistically significant decrease in the mean pain index from 1.74 ± 0.47 at baseline to 0.65 ± 0.71 at the end of 12 weeks with Glu ($p < 0.001$ compared with baseline and placebo). Use of MSM significantly decreased the mean pain index from 1.53 ± 0.51 to 0.74 ± 0.65, and combination treatment resulted in a highly significant decrease in the mean pain index (1.7 ± 0.47 to 0.36 ± 0.33; $p < 0.001$). Combination therapy was more effective in reducing pain compared with individual treatments ($p < 0.05$).

Glu provides good pain relief compared with placebo, as observed on VAS recording. It signifi-

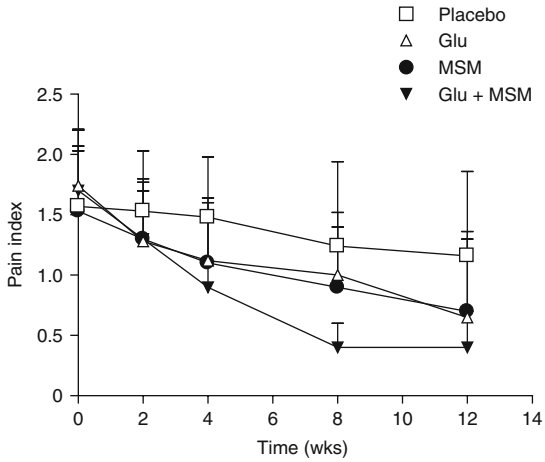

Fig. 1. The effect of the four treatments (glucosamine 500mg and matching placebo of methylsulfonylmethane, one capsule each three times daily; methylsulfonylmethane 500mg capsule and glucosamine matching placebo, one capsule each three times daily; one capsule each of glucosamine and methylsulfonylmethane three times daily; and two capsules three times daily of placebo identical to glucosamine and methylsulfonylmethane capsules) on the pain index. **Glu** = glucosamine; **MSM** = methylsulfonylmethane.

cantly decreased the mean pain intensity from 58 ± 11mm (baseline) to 54 ± 10, 48 ± 11, 42 ± 10 and 39 ± 11mm, while MSM decreased pain intensity from 57 ± 9mm (baseline) to 53 ± 10, 51 ± 10, 46 ± 12 and 38 ± 10mm at the end of 2, 4, 8 and 12 weeks, respectively. The decrease in mean pain intensity on VAS (from 56 ± 12mm [baseline] to 50 ± 9, 44 ± 11, 41 ± 10 and 36 ± 9mm after 2, 4, 8 and 12 weeks, respectively) was much higher with combination therapy compared with placebo and with individual treatments.

At the end of 12 weeks' treatment, the mean swelling index significantly decreased from 1.43 ± 0.63 to 0.52 ± 0.51 with Glu, and from 1.30 ± 0.65 to 0.39 ± 0.50 with MSM, while there was a greater decrease in swelling index with combination therapy, from 1.43 ± 0.63 to 0.14 ± 0.35, after 12 weeks ($p < 0.05$ compared with Glu and MSM alone). There was no decrease in the swelling index with placebo.

The Glu and MSM combination produced significant improvement in joint function with a reduction in pain and swelling. Treatment with Glu, MSM and a combination of the two significantly favourably altered the walking time and joint mobility index compared with placebo. The overall functional ability improved significantly with combination treatment compared with either drug given alone (figure 3).

In the present investigation, we used the Lequesne index to compare the efficacy of Glu and MSM and their combination with placebo, to evaluate the effect on inflammatory, functional and day-to-day activity of the knee joint in osteoarthritis. At baseline all the groups had similar indices suggesting a comparable degree of osteoarthritis. Treatment with Glu and MSM, individually, decreased the Lequesne index significantly from 13 ± 0 to 8.85 ± 3.2, and 12.48 ± 2.25 to 8.48 ± 1.89 ($p < 0.001$) at the end of 12 weeks' treatment, respectively. With combination therapy, the Lequesne index significantly decreased from 13 ± 2.09 to 8.65 ± 3.29 ($p < 0.001$) at the end of 12 weeks of treatment, while with placebo, there was no significant decrease in the Lequesne index (figure 4).

As a secondary efficacy parameter, we also evaluated the consumption of rescue medicine (paracetamol 500mg tablets). For patients who received

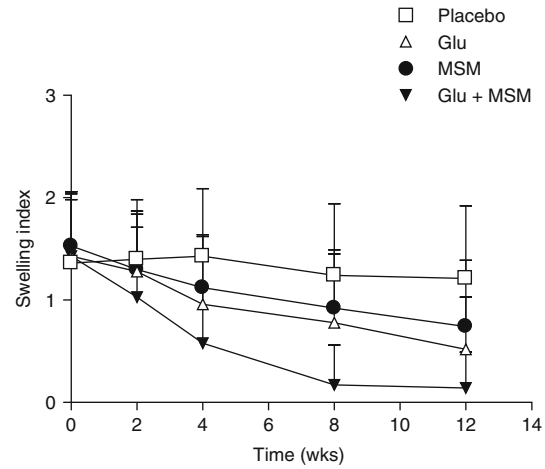

Fig. 2. The effect of the four treatments (glucosamine 500mg and matching placebo of methylsulfonylmethane, one capsule each three times daily; methylsulfonylmethane 500mg capsule and glucosamine matching placebo, one capsule each three times daily; one capsule each of glucosamine and methylsulfonylmethane three times daily; and two capsules three times daily of placebo identical to glucosamine and methylsulfonylmethane capsules) on the swelling index. **Glu** = glucosamine; **MSM** = methylsulfonylmethane.

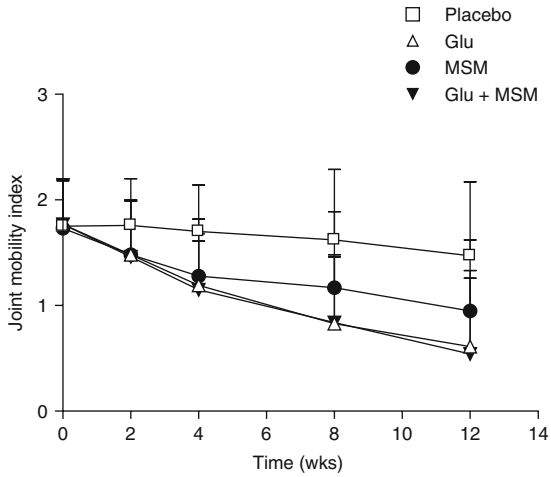

Fig. 3. The effect of the four treatments (glucosamine 500mg and matching placebo of methylsulfonylmethane, one capsule each three times daily; methylsulfonylmethane 500mg capsule and glucosamine matching placebo, one capsule each three times daily; one capsule each of glucosamine and methylsulfonylmethane three times daily; and two capsules three times daily of placebo identical to glucosamine and methylsulfonylmethane capsules) on joint mobility. **Glu** = glucosamine; **MSM** = methylsulfonylmethane.

combination treatment, the use of rescue medicine was less compared with those taking Glu and MSM alone and placebo. In the placebo group, the mean consumption of paracetamol tablets increased from 15 ± 7 to 24 ± 9 at the end of 12 weeks of treatment, while the use of rescue medicine decreased significantly from 13 ± 8 to 8 ± 6 tablets after 12 weeks of combination therapy (figure 5).

During the 12-week treatment, Glu, MSM, combination therapy and placebo were well tolerated by all subjects; except for mild gastrointestinal discomfort, no patient had any serious side effect. The main adverse event was diarrhoea, occurring in >5% patients, and this was more common in the Glu group. None of the patients discontinued therapy due to any adverse drug reaction.

Treatment Compliance

Compliance with treatment was good (81–90% drug consumption) in about 80% of patients in all groups, while in the remaining 20% it was fair. There was no significant difference in compliance with treatment in each group.

Global Evaluation

In global assessment of the treatments, combination treatment was rated as excellent and good by 88% patients, while 82% and 76% of patients evaluated Glu and MSM treatment, respectively, as good and excellent compared with placebo. About 15% of patients receiving placebo rated treatment as fair or good.

Discussion

Osteoarthritis is a typically degenerative disorder presenting two types of problems. On the one hand, pain has to be alleviated because this is the patient's immediate problem. On the other hand, the physician is concerned more about stopping the degenerative process at the earliest stage. Glucosamine treatment appears to cover both aspects. Data from a trial in a small number of patients showed that oral Glu resulted in substantial improvement in patients with osteoarthritis.[23] Reichelt et al. have reported that with intramuscular Glu 400mg twice weekly, an impressive decrease in pain and functional limitation was achieved between the fourth and fifth

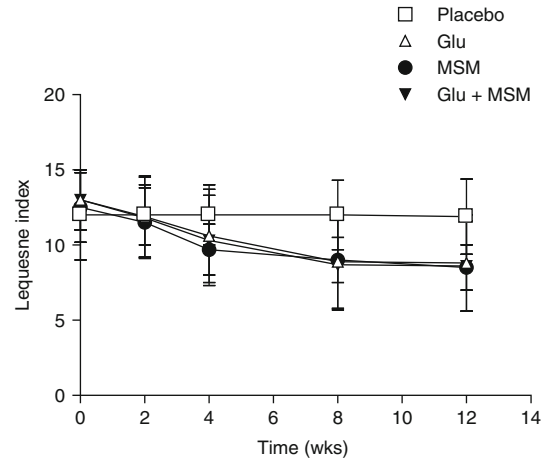

Fig. 4. The effect of four treatments (glucosamine 500mg and matching placebo of methylsulfonylmethane, one capsule each three times daily; methylsulfonylmethane 500mg capsule and glucosamine matching placebo, one capsule each three times daily; one capsule each of glucosamine and methylsulfonylmethane three times daily; and two capsules three times daily of placebo identical to glucosamine and methylsulfonylmethane capsules) on the Lequesne index. **Glu** = glucosamine; **MSM** = methylsulfonylmethane.

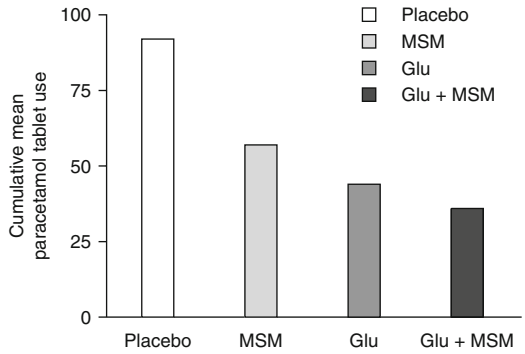

Fig. 5. The cumulative mean number of paracetamol tablets (rescue medicine) consumed in the four treatment groups (glucosamine 500mg and matching placebo of methylsulfonylmethane, one capsule each three times daily; methylsulfonylmethane 500mg capsule and glucosamine matching placebo, one capsule each three times daily; one capsule each of glucosamine and methylsulfonylmethane three times daily; and two capsules three times daily of placebo identical to glucosamine and methylsulfonylmethane capsules). **Glu** = glucosamine; **MSM** = methylsulfonylmethane.

weeks of treatment.[4] Previous studies have shown oral Glu to be a safe and effective slow-acting drug for osteoarthritis. There is evidence that Glu may provide pain relief, reduce tenderness and improve mobility in patients with osteoarthritis.[1]

In the present study, the beneficial effects of Glu developed slowly over time. Although clinical improvement in signs and symptoms of osteoarthritis started to be evident after the second week, it was highly significant from the fourth week onward. This beneficial effect was maintained in the follow-up observation period. This is in accordance with previous studies with Glu as a candidate as a SADOA, in that it selectively relieves osteoarthritis symptoms, with a few weeks delay in the onset of its action, which is then sustained throughout treatment and tends to last until after drug discontinuation.[1-4] There is now good evidence available that symptomatic slow-acting drugs are valuable therapeutic tools for osteoarthritis.[24,25] Several studies have compared Glu with NSAIDs such as ibuprofen. An early European study produced interesting results: after 2 weeks of therapy with ibuprofen, patients experienced less pain than in the Glu group. However, after 8 weeks, the group receiving Glu responded favourably with a significant reduction in pain and swelling, while ibuprofen seemed to be less effective.[26] However, Rindone et al., in their study of Glu versus placebo, concluded that Glu was no better than placebo.[27] The authors explained their negative results on the basis that the patient population was older, heavier and had had arthritis for a longer time, and also on the shorter study duration. Another recent study by Hughes and Carr also concluded that Glu was no more effective than placebo.[28]

At present, there are several studies demonstrating that chondroitin sulfate (CS) is absorbed after oral administration and promotes the modification of a clinical picture of osteoarthritis acting as a symptomatic slow-acting drug.[29,30] In a comparative study of diclofenac sodium versus CS, diclofenac produced a prompt reduction of clinical symptoms, which, however, reappeared at the end of treatment. With CS, the therapeutic response appeared later in time but lasted for up to 3 months after the end of treatment.[31] McAlindon et al. conducted a meta-analysis of the trials published on Glu and CS combination therapy. The authors concluded that trials of Glu and CS preparations for osteoarthritis symptoms demonstrated moderate to large effects.[32] Furthermore, in the present study, combination therapy produced highly significant improvement in parameters of osteoarthritis from the second week onwards; however, the clinical effect produced by the combination was significant compared with that produced by the individual drugs from the fourth week onward.

MSM is an organic source of sulphur. Sulphur is also a vital component of powerful antioxidants such as N-acetylcysteine and reduced glutathione. Damage from oxidative stress can often lead to inflammation and pain. The results of several animal studies have indicated that with MSM supplementation, joint pain was significantly reduced and mobility enhanced.[33,34] In one preliminary double-blind study, 16 patients with degenerative arthritis or joint disease were administered MSM daily for 6 weeks. An 80% reduction in pain was reported.[35] The author suggested that the high sulphur content of MSM may also prove helpful in treating similar diseases such as rheumatoid arthritis, osteoarthritis,

systemic lupus erythematosus and temporal mandibular joint dysfunction. In another study, Jacob and Herschler found that DMSO tended to pass through the skin and carry other materials with it. DMSO also demonstrated pain-reduction and anti-inflammatory properties.[36] Our results are in accordance with these reported studies since in the present study we demonstrated significant decreases in pain and improvement in joint mobility, which was evident by the end of the second week of treatment with MSM and continued up to the end of the treatment.

Perez et al. have suggested that meclofenamic acid, a potent NSAID, specifically inhibits chemotactic factor-induced human polymorphonuclear leucocyte functions: chemotaxis, degranulation and generation of superoxide anion radicals. These effects of the drug were found to be dependent upon the concentrations of drug not bound to albumin (free drug), and were caused by its ability to interfere at both a receptor and post-receptor (i.e. a step distal to mobilisation of polymorphonuclear leucocyte intracellular Ca^{2+}) level. These unique actions of meclofenamic acid may provide a partial explanation for its potent anti-inflammatory effect.[37]

A preliminary study was performed in 16 patients with degenerative arthritis. Ten patients, randomly chosen, were treated with MSM 2250mg per day while six patients received placebo capsules. Eight of the ten patients receiving MSM experienced some relief within 6 weeks, while only one patient showed minimal improvement with placebo.[38]

Preliminary research shows that DMSO applied directly to the skin has anti-inflammatory properties and alleviates pain, including pain associated with osteoarthritis.[39] A recent double-blind study in Germany found that a 25% concentration of DMSO in gel form relieved osteoarthritis pain significantly better than placebo after 3 weeks.[40] DMSO appears to reduce pain by inhibiting the transmission of pain messages by nerves rather than through a process of healing damaged joints.[41] DMSO is available in different strengths and different degrees of purity, and certain precautions must be taken when applying DMSO. For these reasons, DMSO should be used only under the supervision of a doctor. According to a preliminary report, 2250mg per day of MSM, an oral form of DMSO, reduced osteoarthritis pain after 6 weeks in a small double-blind trial.[5]

Combination therapy produced a highly significant reduction in pain intensity and swelling and a decrease in the Lequesne index. MSM, a volatile component in the sulphur cycle, is another source of sulphur found in the human diet. Increases in serum sulfate may explain some of the therapeutic effects of MSM, DMSO and Glu.[38]

The results of the present study indicate that all treatments were well tolerated and the side effects observed were predominantly gastrointestinal effects and did not necessitate withdrawal of treatment. Similar results were reported with earlier studies. In one study, the authors suggested that glycosaminoglycan-peptide complex offers not only an effective but also a well tolerated form of treatment that can be used to replace or supplement NSAIDs, particularly in long-term therapy.[42] Morreale et al. commented that although NSAIDs overcome the painful symptoms of acute inflammation, they are not able to modify the disease itself or its evolution.[31] Furthermore, NSAIDs often present with adverse effects that are predominantly gastrointestinal, which limits their prolonged use in the treatment of chronic degenerative disease. A recent study demonstrated that Glu was as beneficial as ibuprofen for reducing pain and inflammation associated with joint degeneration. However, some adverse reactions, predominantly gastrointestinal intolerance, were reported with ibuprofen, while Glu proved to be well tolerated.[24]

The low toxicological profiles of these sulphur compounds, combined with therapeutic effects, require continued investigation in clinical trials. The present study was conducted at only one centre for 12 weeks. We recommend that a larger multicentre study, carried out for a longer duration, be undertaken in order to establish the efficacy and safety of the combination therapy. As there is very little information in peer-reviewed journals on the use of MSM alone or its combination with Glu in humans,

more clinical trials are warranted to fully assess its therapeutic benefits.

Conclusion

In conclusion, the results of the present study suggest that therapy with Glu, MSM and their combination produced an analgesic, anti-inflammatory effect in patients with osteoarthritis. Combination therapy showed better efficacy in reducing pain and swelling and improving the functional ability of joints than the individual agents. All the treatments were well tolerated. The onset of analgesic and anti-inflammatory activity was found to be more rapid with the combination than with Glu alone. It can be concluded that the combination of MSM with Glu provides better and more rapid improvement in patients with osteoarthritis. However, further studies are warranted for assessing its long-term efficacy and safety.

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Correspondence and offprints: Dr *P.R. Usha*, Department of Clinical Pharmacology and Therapeutics, Nizam's Institute of Medical Sciences, Panjagutta, Hyderabad-500082, India.
E-mail: ushapingali@yahoo.com